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Pancreatic Fluid Interleukin-1β Complements Prostaglandin E2 and Serum Carbohydrate Antigen 19-9 in Prediction of Intraductal Papillary Mucinous Neoplasm Dysplasia

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Abstract

Objectives: We sought to determine if interleukin (IL)-1β and prostaglandin E2 (PGE2) (inflammatory mediators in pancreatic fluid) together with serum carbohydrate antigen (CA) 19–9 could better predict intraductal papillary mucinous neoplasm (IPMN) dysplasia than individual biomarkers alone.

Methods: Pancreatic cyst fluid (n = 92) collected via endoscopy or surgery (2003–2016) was analyzed for PGE2 and IL-1β (Enzyme-Linked Immunosorbent Assay). Patients had surgical pathology-proven IPMN. Threshold values (PGE2 [>1100 pg/mL], IL-1β [>20 pg/mL], serum CA 19–9 [>36 U/mL]) were determined.

Results: Levels of IL-1β were higher in high-grade (HGD)/Invasive-IPMN (n = 42) compared to Low/Moderate-IPMN (n = 37) (median [range], 54.6 [0–2671] vs 5.9 [0–797] pg/mL; $P < 0.001$; Area Under Curve [AUC], 0.766). Similarly, PGE2 was higher in HGD/Invasive-IPMN (n = 45) compared to Low/Moderate-IPMN (n = 47) (median [range], 1790 [20–15,180] vs. 140 [10–14,630] pg/mL; $P < 0.001$; AUC, 0.748). Presence of elevated PGE2 and IL-1β (AUC, 0.789) provided 89% specificity and 82% positive predictive value (PPV) for HGD/Invasive-IPMN. Elevated levels of all three provided 100% Specificity and PPV for HGD/Invasive-IPMN.

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Conflict of Interest: None declared.

Conclusion: Cyst fluid PGE2, IL-1β, and serum CA 19–9 in combination optimize specificity and PPV for HGD/Invasive-IPMN and may help build a panel of markers to predict IPMN dysplasia.

Keywords

intraductal papillary mucinous neoplasm; pancreatic cyst; interleukin-1β; prostaglandin E2; biomarker; dysplasia

INTRODUCTION

Despite an increase in survival rates for other solid tumors, the prognosis for patients with pancreatic cancer remains poor. Pancreatic cancer is now the fourth leading cause of cancer-related death in the United States and is predicted to become the second behind lung cancer by 2030.[1,2] Although many cases of pancreatic cancer occur sporadically in the population, patients with pancreatic cysts are known to be at risk of developing pancreatic cancer.[3] Pancreatic cysts are being diagnosed more frequently due to the widespread use of high-resolution imaging and increased physician awareness of symptoms associated with pancreatic cysts.[4] In fact, pancreatic lesions are incidentally detected in up to 15% of American adults undergoing imaging for an unrelated reason.[5–7]

The most common type of mucinous pancreatic cyst is intraductal papillary mucinous neoplasm (IPMN), clinically noteworthy because it has significant potential to progress to invasive pancreatic cancer. Although the natural history of IPMN is not well understood, these precursor lesions are thought to progress in a stepwise fashion, thereby offering a window of opportunity to intervene prior to malignant transformation. While most IPMNs are low/moderate grade and can be safely monitored as low-risk, high grade (HGD) and invasive IPMN are high-risk for malignant transformation and should be resected in fit patients; however, accurate risk stratification is difficult to achieve pre-operatively. Determination of pancreatic duct involvement (main, branch, or mixed) by imaging or endoscopic ultrasound may identify higher risk main duct or mixed type cysts that are usually recommended for resection,[8] but this alone is often not sufficient to make a definitive, accurate diagnosis of malignancy. Additionally, nearly 30% of IPMN are misclassified preoperatively as involving the main duct when compared to surgical pathology; conversely, 20% of IPMN thought to have branch-duct involvement alone have main duct-involvement on surgical pathology.[9]

To aid in the complex clinical management of IPMN, the International Consensus Guidelines were established in 2006[10] and subsequently revised in 2012.[8] Based upon the assessment of clinical and radiological features, the consensus guidelines demonstrate high sensitivity (>90%) for predicting malignancy but very low specificity (25–30%).[11–14] This low specificity results in potentially morbid pancreatic surgical resection (1–5% mortality, 20–40% morbidity) of low-risk benign IPMN.[15,16] The most recent 2016 revision to the guidelines states that elevated serum levels of the tumor marker carbohydrate antigen 19–9 (CA 19–9 ≥37 U/mL) may be associated with high-risk IPMN, but use of this biomarker is limited by its low specificity and absence in some patients.[17] To improve upon these existing

management algorithms, accurate and reliable biomarkers that correlate with malignant potential or dysplastic grade of IPMN are clearly needed.

Analysis of pancreatic cyst fluid, obtained during endoscopic ultrasound-guided needle aspiration, has gained recent favor to aid in differentiating low- from high-risk IPMN.[18] Although cyst fluid cytology may assist in diagnosing malignancy, it is often inaccurate or non-diagnostic for IPMN dysplasia. A few promising molecular markers (tumor/DNA) in cyst fluid have been identified and validated for clinical use, but to date none correlates with dysplasia or can predict the natural history of the cyst.[18] A concerted research effort is ongoing to identify novel cyst fluid biomarkers with sufficient diagnostic utility. Reflecting the role of inflammation in malignancy, we previously discovered and validated that elevated levels of cyst fluid prostaglandin E2 (PGE2) correlated with IPMN dysplastic grade[19,20]; subsequently, another group provided evidence that the inflammatory cytokine interleukin-1β (IL-1β) was an accurate predictor of HGD/Invasive-IPMN.[21]

In the present study, we sought to externally validate IL-1β as an indicator of IPMN malignant risk in a larger group of patients. In addition, we evaluated the diagnostic performance of IL-1β, PGE2, and currently employed serum CA 19–9 in the same cohort, alone or in combination. We report that the novel combination of these cyst fluid and serum biomarkers is able to better predict high-risk disease warranting surgical resection, while distinguishing low-risk lesions that may safely undergo active surveillance.

MATERIALS AND METHODS

After informed consent was obtained, pancreatic cyst or duct fluid was gathered at the time of preoperative endoscopy (via endoscopic ultrasound guided fine-needle aspiration) or at the time of pancreatic resection (June 2003-August 2016). Aliquots were stored at −80°C and subsequently thawed on ice for biomarker testing. All patients underwent surgical resection with confirmed diagnosis of IPMN, using the World Health Organization criteria to determine dysplastic grade. Patients were divided into two groups based on dysplastic grade: the first group (low-risk IPMN) included those with Low or Moderate-grade IPMN, whereas the second group (high-risk IPMN) included those with HGD or Invasive IPMN.

Demographics and clinical data including preoperative serum CA 19–9 were supplemented through electronic medical record review. Pancreatitis and main pancreatic duct involvement were determined by surgical pathology. Patients using nonsteroidal anti-inflammatory drugs (NSAIDS) during their pre-operative evaluation were considered to be NSAID users. All data were gathered and stored in compliance with the Indiana University Institutional Review Board.

Biomarker Measurement and Analysis

Pancreatic fluid levels of IL-1β and PGE2 were measured using commercially available ELISA kits (Cat#DLB-50; R&D, Minneapolis, Minn and #RPN222; GE Healthcare Life Sciences, Pittsburgh, Penn). PGE2 data for patients included in the present study as well as determination of the optimal PGE2 threshold (>1100 pg/mL) have been published previously.[20] The threshold value of IL-1β (>20 pg/mL) was approximated using Youden's

Index to optimize sensitivity and specificity for high-risk lesions. The cutoff value for CA 19–9 (>36 U/mL) was determined using our institution's reported normal range.

Sensitivity (Sn), Specificity (Sp), Positive Predictive Value (PPV), Negative Predictive Value (NPV), and Accuracy (Acc) of individual biomarkers and combinations were calculated using these defined values. Biomarker levels were compared using the Wilcoxon rank-sum test and receiver operating characteristic (ROC) curve analysis. Descriptive statistics including mean, median, and frequencies were calculated as appropriate. Baseline group characteristics between low- and high-risk IPMN were compared using *t*-test for continuous data and chi-square for categorical data. Pearson correlation was used to determine associations between baseline characteristics and biomarker levels. Multivariable analysis was performed to determine if biomarkers were independent predictors of IPMN dysplastic grade. IBM SPSS Statistics for Windows, Version 24.0 (Armonk, NY) and R Statistical Software, Version 3.4.3 (R Foundation, Vienna, Austria) were used for these analyses.

RESULTS

A total of 92 patients undergoing care for IPMN at Indiana University Health-University Hospital provided informed consent for pancreatic fluid collection at the time of pre-operative endoscopy (n = 23) or pancreatic resection (n = 69). All 92 patients underwent surgical resection with pathology-confirmed diagnosis of IPMN (47 Low/Moderate-Grade, 28 High-Grade [HGD], 17 Invasive). Low-risk (Low/Moderate-Grade) and high-risk (HGD/Invasive) groups were similar in age, sex, and pre-procedural NSAID use (Table 1). On surgical pathology, those with HGD/Invasive-IPMN had a higher incidence of pancreatitis (81.8% vs 63.0%; $P = 0.047$) as well as main pancreatic duct involvement (79.1% vs 44.4%; $P = 0.001$).

Pancreatic fluid levels of IL-1β were significantly higher in patients with HGD/Invasive-IPMN (n = 42) compared to those with Low/Moderate-IPMN (n = 37) (median [range], 54.6 [0–2671] vs. 5.9 [0–797] pg/mL; $P < 0.001$) (Fig. 1A). On ROC curve analysis, IL-1β provided an AUC of 0.766. Similarly, pancreatic fluid concentrations of PGE2 were significantly higher in patients with HGD/Invasive-IPMN (n = 45) compared with Low/Moderate-IPMN (n = 47) (median [range], 1790 [20–15,180] pg/mL vs. 140 [10–14,630] pg/mL; $P < 0.001$), providing an AUC of 0.748 on ROC curve analysis (Fig. 1B). These two pancreatic fluid biomarkers outperformed the currently employed serum CA 19–9 biomarker (AUC, 0.617). Circulating levels of serum CA 19–9 were not significantly different between those with HGD/Invasive-IPMN (n = 42) and Low/Moderate-IPMN (n = 35) (median [range], 28.5 [1–11,755] U/mL vs. 14 [1–497] U/mL; $P = 0.079$) (Fig. 1C). Additionally, if Invasive-IPMN were excluded from analysis, levels of IL-1β as well as PGE2 but not CA 19–9 were significantly higher in HGD-IPMN versus Low/Moderate-IPMN ($P = 0.002$, $P < 0.001$, $P = 0.909$ respectively).

Individual biomarkers (IL-1β or PGE2) were assessed against each clinical variable (age, sex, pancreatitis, NSAID use, main-duct involvement) using Pearson correlation and no significant correlations were detected ($P > 0.05$). On binary logistic regression including IL-1β, PGE2, main-duct involvement and pancreatitis on surgical pathology, main-duct

involvement and PGE2 concentration remained independent predictors of HGD/Invasive-IPMN. IL-1β approached significance as an independent predictor of HGD/Invasive-IPMN ($P = 0.054$).

Beyond individual biomarker performance, we explored whether combinations of IL-1β, PGE2, and serum CA 19–9 would further enhance our ability to distinguish between low- and high-risk lesions. The best two-biomarker model including IL-1β + PGE2 improved the AUC to 0.789 relative to each alone on ROC curve analysis. The three-biomarker model with the addition of serum CA 19–9 increased the AUC slightly to 0.791 (Fig. 2). These stepwise models for individual biomarkers and combinations with associated AUC values are summarized in Table 2.

Using our predetermined threshold values for PGE2 (>1100 pg/mL), IL-1β (>20 pg/mL), and serum CA 19–9 (>36 U/mL), predictive metrics (Sensitivity, Specificity, Accuracy, PPV, NPV) were calculated for the biomarkers alone or in various combinations (using AND/OR statements) as summarized in Table 3. Individually, elevated IL-1β performed better than PGE2, providing respective Sensitivity (64.3%, 60.0%), Specificity (83.8%, 78.7%), Accuracy (73.4%, 69.6%), PPV (81.8%, 73.0%) and NPV (67.4%, 67.3%) in predicting HGD/Invasive-IPMN. Elevation of either PGE2 OR IL-1β resulted in higher Sensitivity (80%), capturing more high-risk IPMNs than each considered alone; Accuracy (75%) and NPV improved (75%) while PPV (75%) and Specificity (69.2%) decreased slightly. Combining IL-1β AND PGE2 enhanced Specificity for HGD/Invasive-IPMN to 89.2%. Elevated serum CA 19–9 in the presence of *either* elevated IL-1β OR PGE2 further enhanced Specificity (96.7%) and PPV (92.9%) for high-risk disease. If the two biomarkers IL-1β AND CA 19–9 or all three biomarkers were elevated above the specified threshold values, Specificity and PPV reached 100.0% with 29 true negatives as well as 11 and 6 true positives, respectively for the two and three biomarkers. We also evaluated these metrics in the presence of elevated IL-1β OR PGE2 OR CA 19–9, and this model provided the highest Sensitivity (88.9%) and NPV (78.3%), with moderate accuracy (69.0%) for predicting high-risk lesions.

DISCUSSION

Given the aggressive nature of pancreatic cancer once established, implementing early detection and prevention strategies in patients who are at risk of developing pancreatic cancer should be a high priority. One such group is patients with IPMN, a known radiographically detectable precursor to pancreatic cancer. Unfortunately, current diagnostic tools used to evaluate and manage IPMN, including radiologic imaging, endoscopic ultrasound, and cyst fluid analyses, are not satisfactory. Pre-operative risk stratification according to recommendations outlined in the International Consensus Guidelines may result in unnecessary major surgery for a benign lesion (overtreatment) or surveillance of a malignant lesion (undertreatment). The challenge is to strike a balance between timely resection of high-risk lesions and avoidance of potentially morbid surgery for those at low-risk. In order to better predict risk of malignant transformation and optimize patient care, additional tools are needed to supplement the existing algorithms.

There are important limitations to current cyst fluid and serum biomarkers for diagnostic testing. The tumor marker CA 19–19 identified in serum has some diagnostic utility in identifying malignancy but lacks sufficient specificity for routine diagnostic use and fails as a test in Lewis antigen-negative patients.[22–24] In direct contact with cells lining the cyst, pancreatic cyst fluid may reflect malignant changes occurring in the lesion; specifically, clues to ongoing events may be revealed upon analysis of cyst fluid biochemical markers, DNA, and cytology.[25] Cytology alone however is often unreliable.[26] Carcinoembryonic antigen (CEA) has been extensively studied and can distinguish between mucinous and non-mucinous cystic lesions (>192 ng/ml) but does not correlate with dysplasia.[27–30] DNA mutations in *KRAS* and *GNAS*, although diagnostic for cyst type, also do not predict malignancy.[29,31,32] Clearly, the search must continue for predictive biomarkers with sufficient sensitivity and specificity for clinical use.

We previously reported that PGE2 levels in pancreatic duct/cyst fluid are elevated in HGD/Invasive-IPMN compared to Low/Moderate-IPMN and subsequently validated this finding in a larger group of patients.[19,20] In the present study, we analyzed levels of pancreatic cyst fluid IL-1β in this same larger cohort and report that IL-1β has higher Sensitivity, Specificity, Accuracy, PPV, and NPV than PGE2 in predicting HGD/Invasive-IPMN. Moreover, IL-1β and PGE2 each individually outperformed serum CA 19–9 as single biomarkers. Despite using different methods of analysis (ELISA vs. ultrasensitive multiplex sandwich immunoassay) and different threshold values, the performance of IL-1β in our hands was similar to that reported by Maker et al,[21] thus externally validating their study of 40 IPMN patients. Respective PPVs for correctly identifying high-risk cysts were 81.8% (our study) and 71% (Maker et al), and respective NPVs for correctly identifying low-risk cysts were 67.4% and 75%.

The presence of either elevated IL-1β OR PGE2 optimizes Sensitivity and Accuracy, allowing for detection of the majority of HGD/Invasive-IPMN pre-operatively, and most frequently categorizes lesions into risk-categories correctly; the addition of CA 19–9 (any of the three) further enhanced Sensitivity. As the number of elevated biomarkers accumulate (PGE2, IL-1β, serum CA 19–9), Specificity and PPV for HGD/Invasive-IPMN increase as high as 100%, so that clinicians can be more certain of the presence of a high-risk lesion requiring resection. Thus, the novel approach of combining these cyst fluid and serum biomarkers may lead to a diagnostic panel that can predict pathology and more accurately direct individual patients to surgery for high-risk lesions versus surveillance for low-risk disease. For IPMN patients under surveillance, changes in biomarker levels in longitudinal samples collected from the same patient may potentially signal increasing dysplasia and thus risk.

We have shown that IL-1β and PGE2 are complementary in their ability to identify high-risk IPMN. As they are both inflammatory mediators, this suggests that inflammatory processes may be occurring within the pancreatic cyst. On the one hand, inflammation is known to play a role in promoting malignant progression; alternatively, tumor growth and development as well as ductal obstruction may result in inflammation. In either case, mediators would be released in association with malignancy as observed in the present study. Interestingly, interleukin-1® has been shown to induce cyclooxygenase-2 expression

and PGE2 secretion in human neuroblastoma cells as well as in human lung fibroblasts.[33,34] Taken together, this suggests that the IL-1β, PGE2, and cyclooxygenase-2, which we previously showed to be overexpressed in precursor lesions known as pancreatic intraepithelial neoplasias and pancreatic adenocarcinomas,[35,36] may be coordinately up-regulated during the malignant progression of IPMN. In support, in many but not all cases, IL-1β and PGE2 were both elevated in the same pancreatic fluid specimen. Pertinent to our study, four other inflammatory pancreatic cyst fluid markers (matrix metallopeptidase 9, cancer antigen 72–4, soluble FAS ligand, interleukin-4) were shown to be elevated in high-risk IPMN and when incorporated into a clinical/radiographic nomogram, demonstrated enhanced predictive performance[37]; this group suggested that anti-inflammatory strategies should be considered to prevent the malignant progression of IPMN, an intervention also supported by our study.

Limitations of the present study are that all patients and pancreatic fluid samples originated from a single institution. Additionally, only patients who underwent surgical resection, and were therefore symptomatic and/or deemed high-risk, were selected for inclusion in order to correlate findings with surgical pathology. Therefore, our results may not be applicable to a more general population of IPMN patients under surveillance who would be candidates for this type of pre-operative diagnostic testing. Finally, larger multi-institution clinical validation studies using prospectively collected specimens must be performed to confirm the utility of these markers as diagnostic tools for management of IPMN.

CONCLUSION

In the present study, we externally validated pancreatic fluid IL-1β as an accurate predictor of IPMN dysplasia. Furthermore, combinations of IL-1β, pancreatic fluid PGE2, and serum CA 19–9 demonstrated improved ability to stratify risk by discriminating HGD/Invasive-IPMN from Low/Moderate-IPMN. Pending further validation, these complementary biomarkers may be useful in a diagnostic panel to supplement current algorithms for the optimal preoperative management of IPMN.

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Abbreviations:

IPMN	Intraductal Papillary Mucinous Neoplasm
IL-1β	Interleukin-1β
PGE2	Prostaglandin E2
CA 19–9	Carbohydrate Antigen 19–9
HGD	High-Grade Dysplasia

AUC	Area Under the Curve
NSAIDS	Nonsteroidal anti-inflammatory drugs
Sn	Sensitivity
Sp	Specificity
PPV	Positive Predictive Value
NPV	Negative Predictive Value
Acc	Accuracy
ROC	Receiver Operating Characteristic
CEA	Carcinoembryonic antigen

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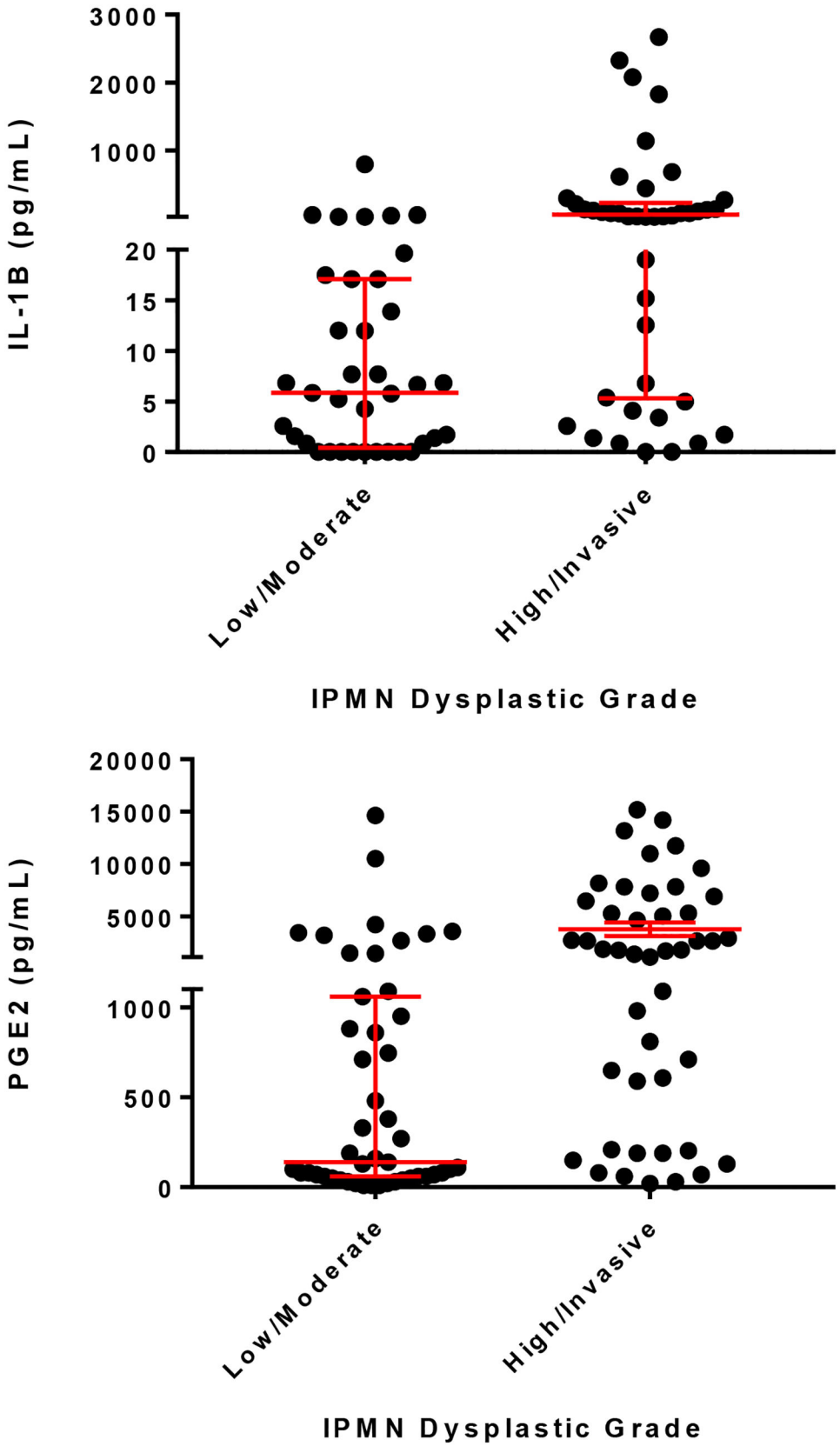

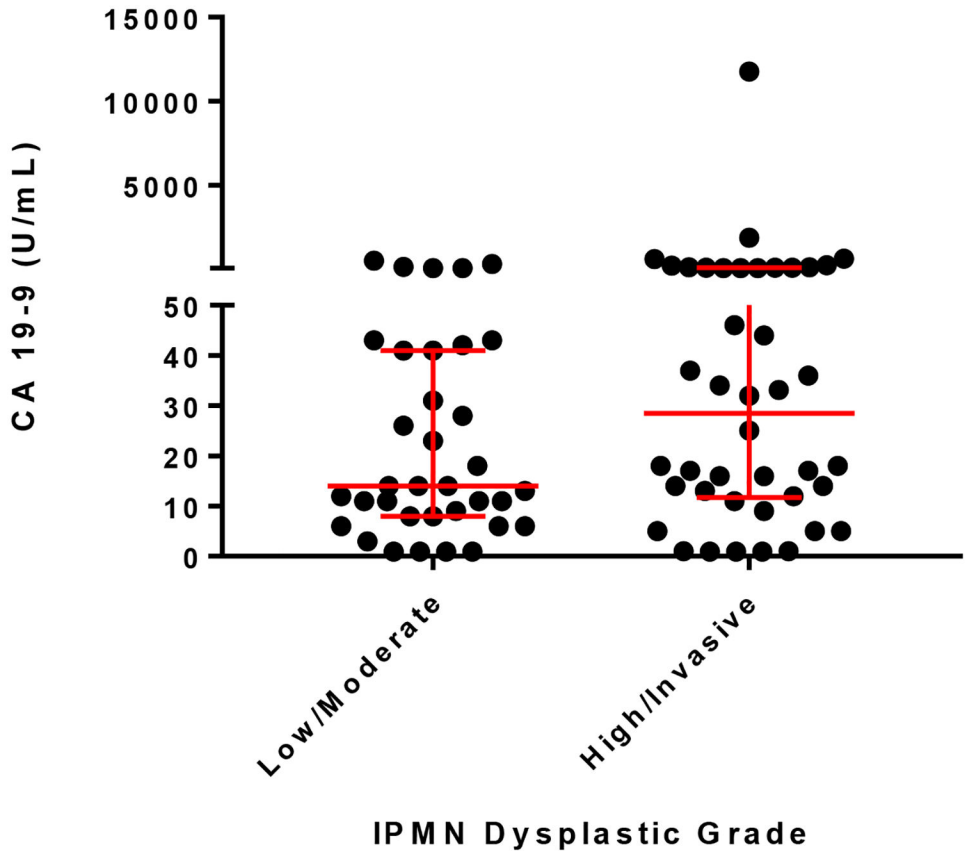

FIGURE 1.

A, Pancreatic fluid IL-1β and IPMN dysplastic grade. The concentration of IL-1β in pancreatic cyst or duct fluid is plotted according to IPMN dysplastic grade. The red error bars represent median +/− interquartile range. The y-axis is discontinuous at 20 pg/mL. B, Pancreatic fluid PGE2 and IPMN dysplastic grade. The concentration of PGE2 in pancreatic cyst or duct fluid is plotted according to IPMN dysplastic grade. The red error bars represent median +/− interquartile range. The y-axis is discontinuous at 1100 pg/mL. C, Serum CA 19–9 and IPMN dysplastic grade. The concentration of serum CA 19–9 is plotted according to IPMN dysplastic grade. The red error bars represent median +/− interquartile range. The y-axis is discontinuous at 50 U/mL.

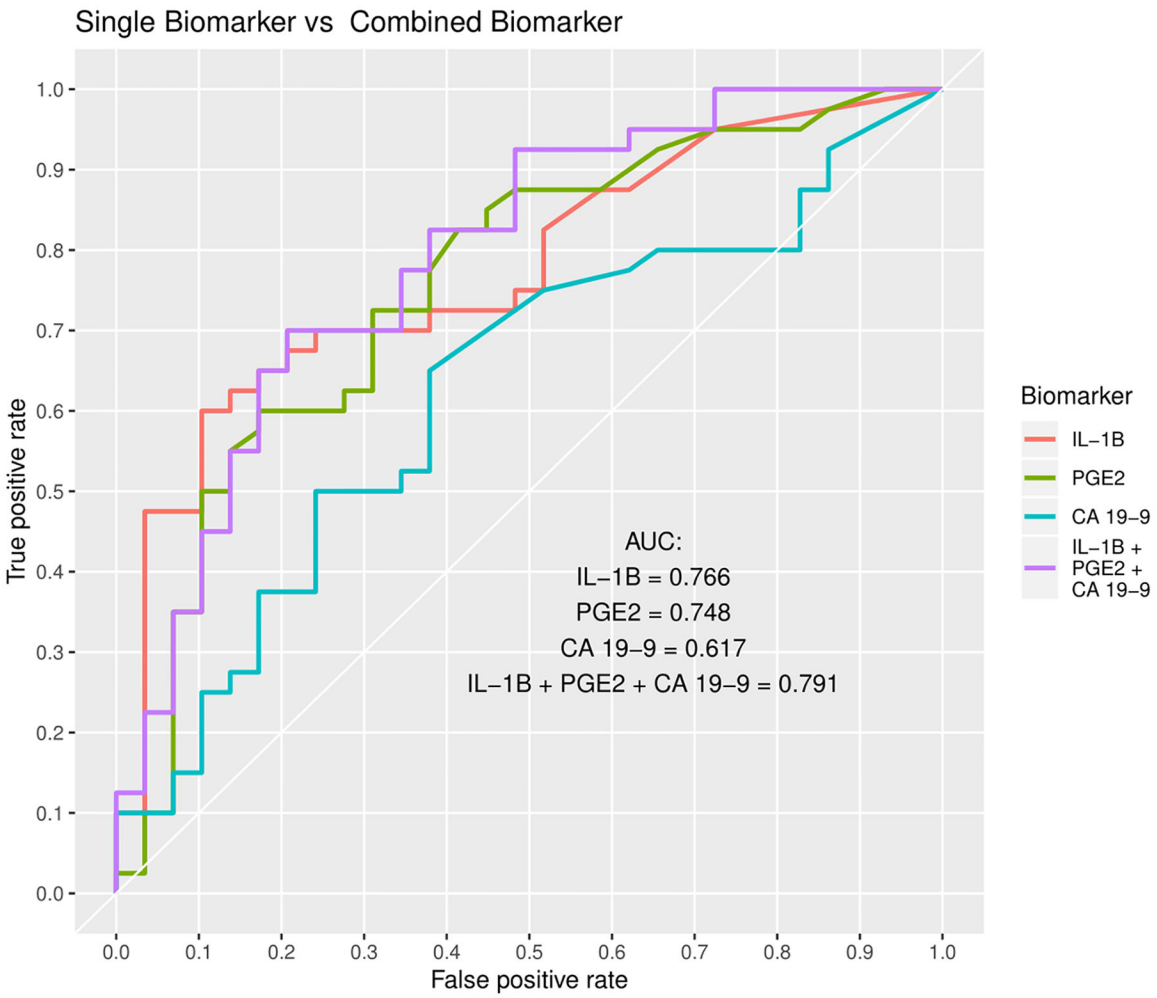

FIGURE 2.

Receiver Operating Characteristic Curve for IL-1β, PGE2, CA 19–9 ROC curves of the three individual biomarkers or combination for predicting high-grade/invasive IPMN are presented.

TABLE 1.

Demographic and Clinical Characteristics of Patients With IPMN, Indiana University Health University Hospital, 2003–2016

Characteristics	Low/Moderate Grade IPMN	High Grade/Invasive IPMN	*P*
Age, n/mean (SD), y	47/68.2 (11.1)	45/66.6 (10.3)	0.466
Sex, n (%)			0.306
Male	18 (38.3)	22 (48.9)	
Female	29 (61.7)	23 (51.1)	
Sample collection method, n (%)			0.547
Endoscopy	13 (27.7)	10 (22.2)	
Surgery	34 (72.3)	35 (77.8)	
Pre-procedure NSAID use, n (%)	15 (31.9)	9 (20.0)	0.193
Pancreatitis, n (%)	29 (63.0)	36 (81.8)	**0.047**
Main-duct involvement, n (%)	20 (44.4)	34 (79.1)	**0.001**

Bold indicates statistical significance with $P < 0.05$

NSAID indicates nonsteroidal anti-inflammatory drugs

TABLE 2.

Predictive Accuracy of Selected Biomarkers for High Grade/Invasive IPMN

Prediction Models	N	AUC
Model 1: IL-1β	79	0.766
Model 2: PGE2	92	0.748
Model 3: CA 19–9	77	0.617
Model 4: IL-1β + PGE2	79	0.789
Model 5: IL-1β + CA 19–9	69	0.758
Model 6: PGE2 + CA 19–9	77	0.769
Model 7: IL-1β + PGE2 + CA 19–9	69	0.791

IL-1β indicates interleukin-1β; PGE2, prostaglandin E2; CA 19–9, carbohydrate antigen 19–9; AUC, Area Under the Receiver Operating Characteristic Curve

TABLE 3.

Summary of Predictive Metrics for Biomarkers, as Individual Components or in Combination

	Sn, %	Sp, %	Acc, %	PPV, %	NPV, %
1 Biomarker					
IL-1β (>20 pg/mL)	64.3	83.8	73.4	81.8	67.4
PGE2 (>1100 pg/mL)	60.0	78.7	69.6	73.0	67.3
CA 19–9 (>36 U/mL)	40.5	71.4	54.5	63.0	50.0
Exactly 1 positive (any 1 of the 3)	32.5	75.9	50.7	65.0	44.9
2 Biomarkers					
IL-1β *or* PGE2	80.0	69.2	75.0	75.0	75.0
IL-1β *or* CA 19–9	76.7	52.9	66.2	67.3	64.3
PGE2 *or* CA 19–9	80.0	52.5	67.1	65.5	70.0
IL-1β *and* PGE2	42.9	89.2	64.6	81.8	57.9
IL-1β *and* CA 19–9	27.5	100.0	58.0	100.0	50.0
PGE2 *and* CA 19–9	19.0	97.1	54.5	88.9	50.0
Exactly 2 positive (any 2 of the 3)	40.0	86.2	59.4	80.0	51.0
(IL-1β *or* PGE2) *and* CA 19–9	31.0	96.7	58.3	92.9	50.0
3 Biomarkers					
IL-1β *and* PGE2 *and* CA 19–9	15.0	100.0	50.7	100.0	46.0
IL-1β *or* PGE2 *or* CA 19–9	88.9	46.2	69.0	65.6	78.3

IL-1β indicates interleukin-1β; PGE2, prostaglandin E2; CA 19–9, carbohydrate antigen 19–9; Sn, Sensitivity; Sp, Specificity; Acc, Accuracy; PPV, Positive Predictive Value; NPV, Negative Predictive Value.